Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 11/1/2019 8:10:07 PM
To: Jerry Campbell [JCampbell@ramboll.com]; Harvey Clewell [HClewell@ramboll.com]
CC: Walsh, Patrick [patrick-walsh@denka-pe.com]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Cascio, Wayne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a1bd931ca2f84ea8ac2f4c44538f3589-Cascio, Wayne]; Jones, Samantha [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=eac77fe3b20c4667b8c534c90c15a830-Jones, Samantha]; Lavoie, Emma [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ac7844f12646c095e4e9093a941623-Lavoie, Emma]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Kirby, Kevin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cbb65672f6f34545be460a66ff6fa969-Kirby, Kevin]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Morozov, Viktor [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=03cc9abb639c453fabc2bbb3e4617228-Morozov, Viktor]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; White, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4e179825823c44ebbb07a9704e1e5d16-White, Paul]; Hawkins, Belinda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=075561d171e845828ec67a945663a8e6-Hawkins, Belinda]
Subject: RE: Chloroprene PBPK: Peer review charge questions

I'm mostly off this afternoon…

I think that the exact BW used won't make much of a difference. But if we are using an average/standard BW for human IVIVE, would it be more appropriate to do likewise for rodents? Maybe not, but then the BWs for the 1-CEO clearance calcs should be changed to match these.

-Paul

From: Jerry Campbell <JCampbell@ramboll.com>
Sent: Friday, November 01, 2019 12:50 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Hi Paul,

Harvey's at a meeting today and won't be back in the office until Monday. We'll go over the calculations for QPC/QCC and get back to you then. I'll see if I can trace the source for the IVIVE BW values for mouse and rat. I'm pretty sure we took those from Yuching's original IVIVE work assuming they were provided by Himmelstein.

Regards,

Jerry Campbell

Managing Consultant

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Friday, November 1, 2019 11:08 AM
To: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Jerry, Harvey, all,

First QA questions. ☺

In the model report section on plethysmography, the average ventilation measured is 56.2 mL/min in 22 g mice. The QPC is then calculated using an assumed ratio of 2/3 for alveolar/total ventilation, right? I can match 39.4 L/h/bw3/4 given that value. And from that I confirm QCC = 27.2 L/h/bw^0.75, using the ratio of 1.45.

First question: But in Fmouse_InVivo.R, we have:
parms["QPC"]<- 37.6 #measured in the study
parms["QCC"]<- 25.9 #V/Q Ratio Marino et al. 2006
Where does QPC = 37.6 come from? (The QCC corresponds to V/Q = 1.45, given that.)

The report notes that QCC = 27.2 is close to the value obtained from the Marino DCM study, 24.2. But 27.2 is a lot larger than the value used for internal metric calculations, 20.1. Is it reasonable to expect that animals in a nose-only system will have cardiac output (and respiration) 35% higher than those in tox study exposures?

Second, Table S-1 lists BWs for mice and rats as 0.03 and 0.25 kg, citing Brown et al., same weight for males and females. But the IVIVE calculations (Supp D) use 0.035 and 0.04 kg for female and male mice, and 0.33 and 0.45 kg for female and male rats, respectively. The discrepancy vs. default value range from 17% to 50%. Are these study-specific BWs, and if so, which specific study? I think they should be the BWs for the animals from which the tissues were collected for the in vitro studies, but this should be stated in the spreadsheet comments. However, I looked but didn't see BWs in Himmelstein et al.

The _metric scripts use the default BW values in Table S-1… So BW^0.75 scaling is then being used to scale metabolism to the standard BW used to calculate the internal metrics, or 22 g of the animals used in the in vivo dosimetry study. (Those were female mice? This isn't said in the report.)

Note: if we have study-specific BW values for the tox studies being analyzed, those should be used rather than default BWs. I don't think this needs to be done in the report, since what's being shown are example calculations, we aren't at the point of full risk extrapolation. But if EPA does use the model, study-specific animal BWs would be more appropriate.

-Paul

From: Jerry Campbell <JCampbell@ramboll.com>
Sent: Wednesday, October 30, 2019 11:24 AM
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Subject: RE: Chloroprene PBPK: Peer review charge questions

Paul,

You were correct. The sensitivity runs had been completed in the acslX version and the files had not been included. I've created the scripts that run each of the three sensitivity simulations and a spreadsheet that includes the SA coefficients calculations and bar charts for the report. The zip file name is chloroprene_model_SA.zip and you can download it from the dropbox folder where we shared the model files. The scripts should run in the version of the model you have. Let me know if you have any questions or if something was off when you tried to run the files.

Regards,

Jerry Campbell

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Friday, October 11, 2019 4:58 PM
To: Jerry Campbell <JCampbell@ramboll.com>; Harvey Clewell <HClewell@ramboll.com>
Cc: Walsh, Patrick <patrick-walsh@denka-pe.com>; Thayer, Kris <thayer.kris@epa.gov>; Cascio, Wayne <Cascio.Wayne@epa.gov>; Jones, Samantha <Jones.Samantha@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Kirby, Kevin <KIRBY.KEVIN@EPA.GOV>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; White, Paul <White.Paul@epa.gov>; Hawkins, Belinda <Hawkins.Belinda@epa.gov>
Subject: RE: Chloroprene PBPK: Peer review charge questions

Jerry, Harvey,

I'm not seeing scripts to run the sensitivity analyses, results in Figures 6 and 7, and plot in Figure 8. None of these is very hard, but things add up. Do you have those?

Also, in Table 1 and the small table on p. 21, the lowest mouse exposure should be 12.8 ppm, not 12.3, right?

-Paul

From: Jerry Campbell <JCampbell@ramboll.com>
Sent: Wednesday, October 09, 2019 11:54 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
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Subject: RE: Chloroprene PBPK: Peer review charge questions

Paul,

You are absolutely correct. The figure you derived from the model is the correct figure for the female mouse in vivo study. I had hoped to determine the source of the incorrect figure but I do not have a version of the model going back to Yuching's original model that generates the figure included in the report so I am at a loss to explain the origin. It is my fault it wasn't updated in the final report. I have corrected the report figure but it sounds like we should hold off on sending you the revision in case any other questions need to be addressed as you complete your QA.

Regards,

Jerry Campbell

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Monday, October 7, 2019 1:34 PM
To: Harvey Clewell <HClewell@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>
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Subject: RE: Chloroprene PBPK: Peer review charge questions

Harvey, Jerry, all,

I assume the draft charge questions have been sent to you by now. I realized there's a mistake in the 2nd question in the section titled, "Estimation of Metabolic Parameters from In Vitro Metabolism Experiments." I had thought that the data (and model parameters) used were from male mice (data in original Himmelstein papers, 2004), but I now realize these are female mouse data! I've also run into an issue with reproducing those model results.

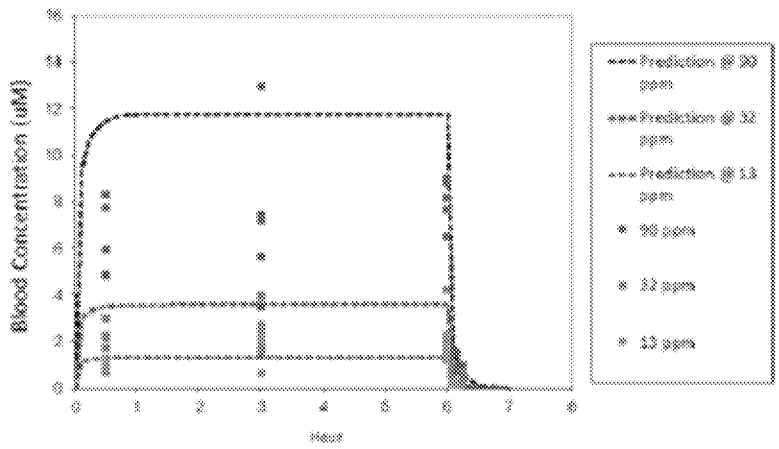
A bit more of an introduction to the question may be helpful, pointing out that these are female data and predictions, but I thought also that the review could be helped by showing predictions for both male and female mouse parameters, to demonstrate the impact of the sex difference.

Setting up to create such a plot, I have hit upon a QA issue: the results I get using the script Fmouse_InVivo.R do not match those shown in Figure 4 of the report. First below is Figure 4 (left panel), 2nd is the plot I first got from just running Fmouse_InVivo.R (files dated 7/16/2019), and third includes dashed lines with predictions using male mouse metabolic parameters. The simulations I'm getting with the package are a lot higher than those shown in the report, which look more like Excel plots in format.

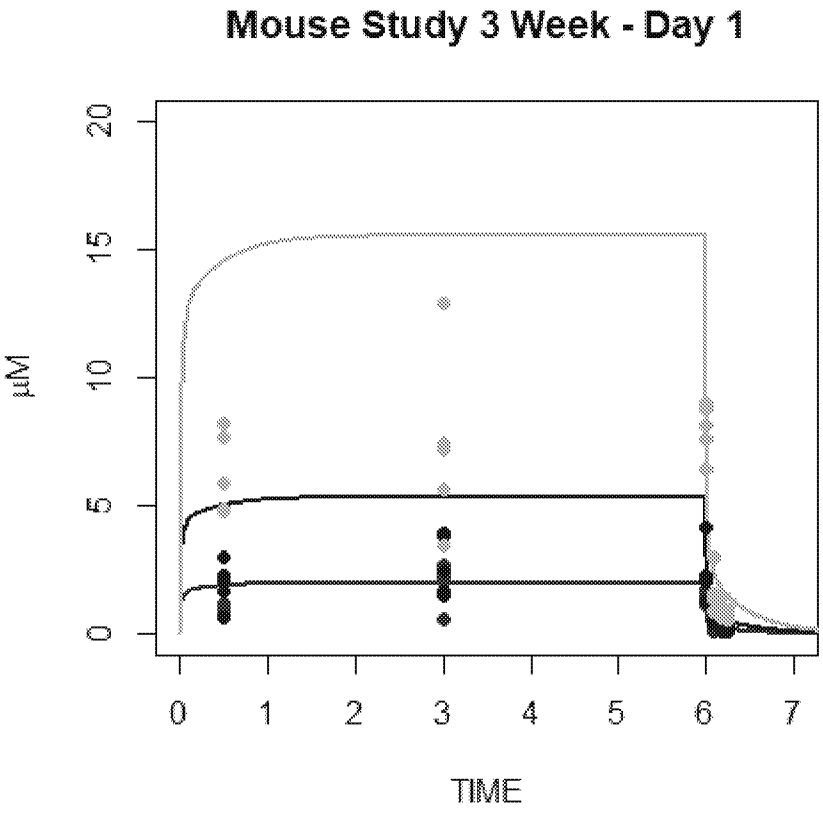
Our intention was to do the QA as the peer review contract was being set up. I'll have to complete my review as soon as possible, so we can resolve any such discrepancies before the material is sent to the reviewers.

-Paul

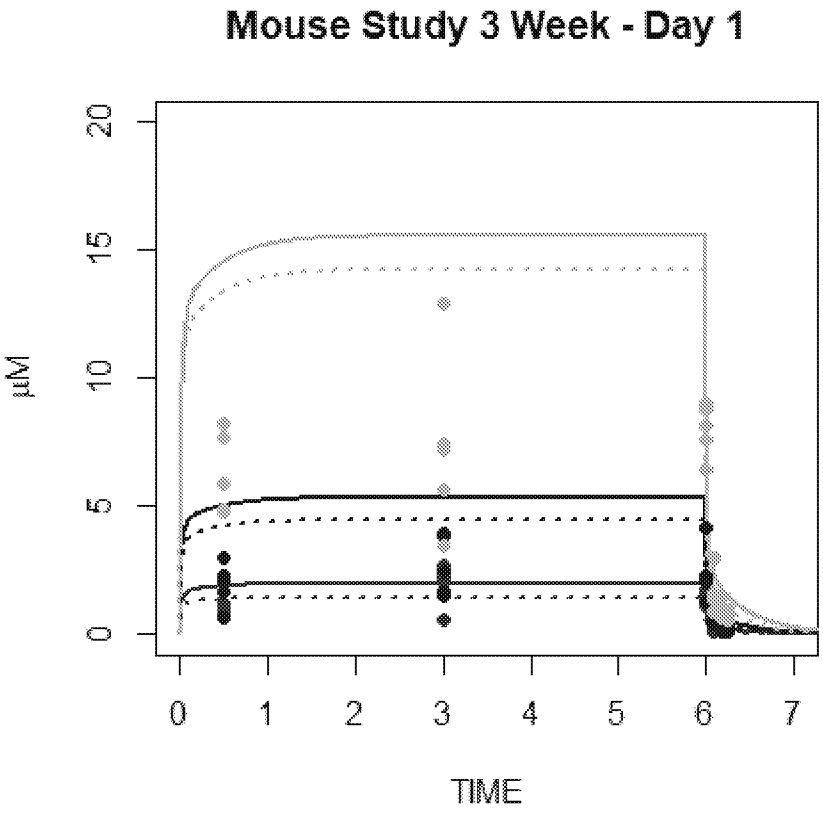
Figure 4 (left panel) from report:



Fmouse_InVivo.R:



Fmouse_InVivo.R with simulations using male mouse parameters (dashed lines) added:



From: Vandenberg, John <Vandenberg.John@epa.gov>
Sent: Wednesday, October 02, 2019 4:46 PM
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Subject: Chloroprene PBPK: Peer review charge questions
Importance: High

Patrick,

We've been diligently evaluating the Ramboll report and conducting analyses related to physiologically-based pharmacokinetic parameters and modeling of chloroprene (references below).

We are moving forward to arrange through a contractor an independent letter peer review by appropriate experts.

In addition to the Ramboll report, we are providing an EPA analysis that we wish to have peer reviewed.

Per our discussion early this summer, we are providing for your information the attached draft Charge questions that will be addressed by the peer reviewers, plus an EPA analysis that we have developed.

Please let us know within a week (by next Wednesday) if you have any major comments on the Charge questions. We are not seeking any comments on the EPA analysis.

Thank you,

John

John Vandenberg, PhD
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References:

Ramboll. (2019). Incorporation of in vitro metabolism data in a physiologically based pharmacokinetic (PBPK) model for chloroprene.

U.S. EPA. (2019). In Vitro to In Vivo Extrapolation (IVIVE) of Metabolism and Non-Enzymatic Conjugation of (1-chloroethenyl)oxirane (1-CEO) and Estimation of Total 1-CEO Clearance in the Liver and Lung of Mice, Rats, and Humans.